

## HEART

*Editorial***Atrial fibrillation: towards an understanding of initiation, perpetuation, and specific treatment**

Atrial fibrillation is the most prevalent cardiac arrhythmia, affecting 0.9% of the general population, including 6% of those over 65 years of age,<sup>1</sup> and its prevalence is increasing.<sup>2</sup> Although structural heart disease underlies most cases, the pathogenesis of atrial fibrillation in the otherwise normal heart—lone atrial fibrillation—is largely unknown. Atrial fibrillation in an apparently normal heart may account for up to one third of all cases, particularly in younger patients.<sup>2</sup> Despite substantial mortality, morbidity, and consumption of health care resources, specific treatment of the arrhythmic source in atrial fibrillation, and the maintenance of sinus rhythm, have remained elusive. Other tachyarrhythmias may be amenable to percutaneous catheter ablation by application of radiofrequency energy to destroy a small region of endomyocardium that is critical to initiation or maintenance of the arrhythmia.

**Initiation of atrial fibrillation**

Recently, clinical and experimental studies have indicated that rapid repetitive activation of the atrial myocardium may play a role in the genesis of atrial fibrillation.<sup>3</sup> It has long been recognised that patients with a variety of regular tachycardias involving the atria, such as accessory pathway mediated junctional reentrant tachycardia, can have an associated tendency to atrial fibrillation, which may be abolished by successfully ablating the underlying arrhythmia. Although this observation has remained largely unexplained, it raises the question of whether the tendency to atrial fibrillation may be causally related to the frequency of atrial myocardial activation during tachycardia. This concept is reinforced by a recent report of an unusual cohort of patients with recurrent atrial fibrillation who can be cured by radiofrequency ablation of a rapidly discharging focal atrial tachycardia that is underlying and apparently “driving” the fibrillation.<sup>4</sup> This small subset of patients so far identified as having atrial fibrillation that can be cured by focal ablation to a single atrial site have a characteristic phenotype: young, of either sex, with no structural heart disease, frequent episodes of intermittent atrial fibrillation interspersed with a distinct rapid atrial tachycardia, and isolated atrial extrasystoles from the same focus typically found to be near the ostia of the pulmonary veins or venae cavae.<sup>4</sup>

**Perpetuation of atrial fibrillation**

Experimental studies support the concept that prolonged rapid atrial activation promotes atrial fibrillation, but also suggest that atrial fibrillation itself causes changes within the atrial myocardium that further promote the perpetuation of the fibrillation.<sup>5-6</sup> That atrial fibrillation begets atrial fibrillation<sup>5</sup> in this way has been demonstrated in animal models,<sup>5-7</sup> and is mediated by progressive atrial electrophysiological remodelling characterised principally by shortening and loss of rate adaptation of the action poten-

tial, resulting in shortening of atrial refractoriness. These changes promote atrial fibrillation by enabling the atrial myocardial mass to accommodate the requisite number of simultaneously propagating wavefronts to ensure perpetuation of the arrhythmia. Conversely, sinus rhythm begets sinus rhythm,<sup>5</sup> and the more sinus rhythm can be maintained after a period of atrial fibrillation, the greater the resolution of the arrhythmic tendency and presumably the pathological remodelling process. This concept is borne out by the clinical observation that cardioversion has a higher success rate and is associated with a greater likelihood of maintaining sinus rhythm when done within the first 24 hours of onset of the arrhythmia.<sup>8-9</sup>

Atrial fibrillation can readily be induced in the normal human heart by rapid atrial pacing, but these episodes are usually brief and non-sustained. This observation indicates that the substrate for atrial fibrillation (albeit non-sustained) exists in the human heart that has not undergone any remodelling. That some patients develop clinical episodes of atrial fibrillation, which may be prolonged or even persistent, in an otherwise apparently normal heart indicates that the atrial myocardium of these individuals has enhanced susceptibility to maintaining the arrhythmia. What determines this susceptibility is unknown. However, the fascinating recent finding of a mutation in the 10q22-q24 chromosomal region in a family with the rare familial atrial fibrillation,<sup>10</sup> raises the possibility that a susceptibility to atrial fibrillation in sporadic cases with an otherwise normal heart may also, at least in part, be genetically determined. This possibility has yet to be investigated.

**Atrial fibrillation in the structurally normal human heart: a hypothesis**

All the recent clinical and laboratory findings combine to provide a compelling, if somewhat challenging, hypothesis for the initiation and perpetuation of atrial fibrillation in the structurally normal heart, which, if proved, may provide a possible framework for understanding and managing this arrhythmia. That is, atrial fibrillation triggered by an atrial tachyarrhythmia, which may initially be focal, induces atrial remodelling in susceptible individuals leading to a perpetuation of the tendency to fibrillation.<sup>3</sup> The reason some patients experience paroxysmal atrial fibrillation and others rapidly progress to having chronic persistent atrial fibrillation may relate to the duration and periodicity of the early arrhythmic episodes and the rate of progression and regression of the atrial remodelling during and between arrhythmic episodes.

According to this hypothesis, once atrial fibrillation is established, the apparently random propagation of multiple simultaneous wavelets of reentrant activity within the atrial myocardial mass<sup>11-12</sup> would mean that any evidence of an underlying focal or regular tachycardia involving the

atria might tend to be lost in the advanced fibrillatory activity and remodelling of the atria. However, patterns of right atrial activation in patients with chronic atrial fibrillation have revealed that atrial activation, even in the chronic phase, is not entirely random and may have a repetitive pattern suggesting some organisation of atrial activation in most cases.<sup>13</sup> Furthermore, in a proportion of patients in whom atrial fibrillation is terminated by the largely experimental procedure of creating multiple lines of conduction block throughout the atria by linear catheter ablation, when fibrillation ceases a persistent focal atrial tachycardia is revealed.<sup>14</sup>

### Specific treatment for atrial fibrillation?

At present, unless there is separate and distinct electrocardiographic evidence of an atrial tachycardia, in most cases there is no means of determining whether a focal arrhythmia is underlying atrial fibrillation in a structurally normal heart. However, the small cohort of patients with the clinical and electrocardiographic characteristics of those identified as having atrial fibrillation cured by ablation of a single focus,<sup>4</sup> should now be considered for electrophysiological investigation in early course, with a view to curative ablation if a focus can be identified.<sup>4</sup> What is also apparent is that the evidence that the natural history of the arrhythmic tendency may be modified if episodes of atrial fibrillation can be terminated early<sup>5-9</sup> should add particular impetus to therapeutic strategies for early cardioversion from atrial fibrillation, such as the implantable atrial defibrillator.<sup>15</sup>

In summary, a number of recent important observations on the pathophysiology of atrial fibrillation are testament to the renewed interest in this arrhythmia, which has long been known to be characterised by multiple wavelets of reentrant atrial activity, but which has proved a resistant clinical challenge. These recent observations provide insight into the causative mechanism underlying the genesis and natural history of atrial fibrillation, and accord

with (but do not prove) the hypothesis that random wavelet reentry may be promoted in the otherwise normal heart by a tachycardia induced atrial myopathic process in susceptible individuals, and that atrial fibrillation so initiated is self-perpetuating as a result of further remodelling of the fibrillating atrium.

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